REMARKS

Claims 1-8 and 44-57 are under examination and claims 9-43 are withdrawn from further consideration as being drawn to non-elected inventions. Claims 1, 44 and 50 have now been amended. New claims 58-65 have now been added to further clarify the scope of the present invention. Claims 1-65 are now under active prosecution in the present application.

Applicants respectfully assert that all amendments are supported by the original disclosure and do not introduce new matter. Moreover, Applicants further respectfully assert that the amendments merely clarify the scope of the claims.

The Examiner contends that claims 3 and 52 comprises species that is distinct from the one originally claimed because the originally claimed structure analogs of phosphatidylserine is dioleolphosphadylserine (see previous claims 3 and 52). The newly submitted claims 3 and 52 comprises phosphatidic acid, phosphatidylglycerol, phosphatidylinositol, palmitoyloleoylphosphatidylserine, palmitelaidoyloleoylphosphatidylserine, myristoleoyloleoylphosphatidylserine, dilinoleoylphosphatidylserine, palmiticlinoleoylphosphatidylserine, lysophosphatidylserine, and dioleoylphosphatidylserine.

The Examiner notes that dioleoylphosphatidylserine has been constructively elected and the other structure analogs of phosphatidylserine listed in claim 3 and 52 are withdrawn from consideration as being directed to a non-elected invention.

The Examiner also contends that due to restriction and species election, claims are now examined to the extent that the inner leaflet component is phosphatidylserine, phosphatidylethanolamine, or a structure analog of phosphatidylserine wherein the structure analog of phosphatidylserine is dioleoylphosphatidylserine.

Applicant will amend claims 3 and 52 to conform to the claims as finally allowed regarding decription of the inner leaflet component as phosphatidylserine or a structural analog thereof.

Applicants appreciate the Examiner's withdrawal of the rejection of claims 2, 5, and 7 under 35 U.S.C. 112, second paragraph, in view of applicant's amendment to the claims.

Claim Rejections - 35 USC § 112, 1st paragraph

The Examiner has maintained her rejection of claims 1 -8 and 50-57 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The Examiner contends that Applicants have provided sufficient detailed examples in the specification showing peptides comprising less than the full amino acid protein depicted in SEQ ID NO:1 and 2. However, the Examiner correctly notes that the US Patent Office clearly does not require a description of every embodiment for peptide claims. It is well known in the art that the proteins of the invention may be altered in various ways including the amino acid substitutions, deletions, truncations, and insertions. Moreover applicants have provided sufficient detail of particular patentable embodiments and a person skilled in the art can easily ascertain the sequences that fall within the scope of the present claims.

The Examiner contends that the instant specification may provide an adequate written description of a genus of polypeptide by structurally describing representative homologues, fragment or variants by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Applicant respectfully points out that the instant specification has done just this.

The polypeptides of the present invention are not just any polypeptide. They are limited by the functional characteristics of polypeptides retaining plasma membrane affinity. This functional characteristic is a feature coupled with a known correlation between this function and structure. It is well known in the art that the plasma membrane affinity is contained in the fusogenic domain of SEQ ID NO:1 and 2. This domain consisted of the first and second helical sequences.

See further description in the references by Qi *et al., J. Biol. Chem.* 271(1996)12, 6874–6880 and *Archives of Biochemistry and Biophysics*, 424, (2004)2, 210-218, entitled Fusogenic domain and lysines in saposin C, and available online 11 March 2004. (References attached)

While Applicant disagrees with the assertion that this is necessary for patentability, the Examiner contends that the specification fails to describe the core structure feature that is correlated to the claimed function (retain plasma membrane affinity). However, as shown in the references described above, adequate guidance is given when the present specification is viewed in light of the known art. That is, the specification and prior art provide functional characteristics coupled to structural features in showing that the helical peptides in saposin C, H-1, and H-2 [saposin C (24–40)] show dominant effects on membrane reorganization..

In order to facilitate an expedited allowance, Applicants have now amended the claims to more narrowly define the variants of the polypeptide. Support can be found in paragraphs 0027 through 0031.

Double Patenting

The Examiner has maintained the rejection of claims 1-3, 44-47 and 50-52 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 16, 17, 21 and 22 of U.S. Patent No. 6,872,406 in view of Vaccaro et al. (FEBS Lett. 1994, 349: 181-186, IDS). Applicants assert that a Terminal Disclaimer will be filed if conflicting claims are issued.

Double Patenting

The Examiner has maintained the provisional rejection of claims 1-3, 44-47 and new claims 50-52 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 16, 17, 21 and 22 of copending Application No. 10/967,921 in view of Vaccaro et al. (FEBS Lett. 1994, 349: 181-186, IDS). Applicants assert that a Terminal Disclaimer will be filed if conflicting claims are issued.

Claim Rejections - 35 USC § 103

The Examiner has rejected claims 1-8, and 44-57 under 35 U.S.C. 103(a) as being unpatentable over Vaccaro et al. (FEBS 1993, 336(1): 159-162) in view of the teachings of O'Brien et al. (W09503821A1), as evidenced by Vaccaro et al. (FEBS, 1994, 349: 181-186, IDS) is maintained.

As previously described, the teachings of Vaccaro and O'Brien show forming liposomal vesicles and then adding saposin C to the formulation, resulting in a surface interaction of the protein with the vesicles. The lipid/saposin vesicle formed by this method will not function the same and will not exhibit anti-tumor activity as with the vesicles of the present invention.

The Examiner claims that the instant specification does not teach that only the nanovesicle form of PS/Sap C has antitumor activity (see specification, page 21, paragraph [0071]). For example, in Working Examples, the PS together with Sap C that are not in nanovesicle form show antitumor activity.

Applicants are confused by this paragraph and respectfully ask for clarification. There is no page 21 of the current application and paragraph [0071] on page 8 is a description of nanovesicle size.

New Grounds of Objections and Rejections

Claim 50 is objected to because of the following informalities: Claim 50 has a typographical error. The word "rcontacted" on line 5 should spell "contacted". Appropriate correction is required. Claim 50 has now been amended to correct this typographical error.

Claim 50 has now been amended to correct this typographical error.

Claim Rejections - 35 USC § 112, 2nd paragraph

The Examiner has rejected claims 44-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 44 recites the limitation "the prosaposin related polypeptide and the inner leaflet component" on line 5. There is insufficient antecedent basis for this limitation in the claim.

Claim 44 has now been amended to correct this antecedent error.

Claim Rejections - 35 USC § 112, 1st paragraph

The Examiner has rejected claims 1-9, and 44-57 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the invention(s), at the time the application was filed, had possession of the claimed invention. This is a **New Matter** rejection.

The term "are contacted with an acidic buffer" recited in claims 1, 44, and 50 is considered new matter since the specification, drawings and claims as filed disclose only "McIlvanine buffer (pH 4.7)". There is no clear support for "acidic buffer". The term "acidic buffer" changes the scope of the invention as originally disclosed. The invention as originally filed disclose one specific acidic buffer i.e. McIlvanine buffer. By using the term "acidic buffer", applicants are claiming any and all acidic buffers.

The claims 1 and 44 have now been amended to cancel this matter.

Thus, is respectfully submitted that the present specification fully meets the requirements of 35 U.S.C. 112 and withdrawal of these rejections is respectfully requested.

Claim Rejections - 35 USC § 103

The Examiner has rejected claims 1-8, and 44-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vaccaro et al. (FEBS 1993, 336(1): 159-162) in view of the teachings of O'Brien et al. (W09503821A1), Vaccaro et al. (FEBS, 1994, 349: 181-186, IDS), and Egas et al. (J. Biol. Chem. 2000, 275(49): 38190-38196).

The teachings of Vaccaro et al. (1993), O'Brien and Vaccaro (1993) have been set forth before in a previous office action. Vaccaro (1993) and O'Brien do not teach the lipid is phosphatidylethanolamine. However, the Examiner contends that these deficiencies are made up for in the teachings of Vaccaro et al. (1994) and Egas et al.

Vaccaro (1994) teaches mixing Sap C and PS (phosphatidylserine) vesicles in 10 mM acetate buffer (pH 4.5-6.0) and incubating at 37°C for 30 min (see page 182, left column, section 2.5). The PS vesicles are small unilamellar vesicles (SUV) or large unilamellar vesicles (LUV) (see page 182, left column, section 2.4). Vaccaro (1994) teaches that Sap C induces leakage of PS containing liposome at low pH (see page 182, left column, section 2.7, and page183). Vaccaro (1994) teaches adding Sap C to the liposome (LUV and SUV vesicles) that contain both N-NBD-PE and N-Rh-PE at acidic condition (see page 182, section 2.6 and 3.1).

Egas et al. teach that the saposin-like domain of the plant aspartic proteinase precursor induces leakage of both PA/PE and PA/PE/PS (phosphatidic acid/phosphatidylethanolamine/phosphatidylserine) vesicles at low pH (see page 38192, right column, last paragraph). Egas et al. teach that this effect was dependent on phospholipid composition, with higher leakage activity in the presence of PA/PE/PS vesicles.

The Examiner now contends that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the assay of Vaccaro (1993) to study the effect of Sap C in combination of different phospholipids, such as PA/PE/PS, on the stimulation of glucosylceramidase activity in view of the teachings of Vaccaro (1994) and Egas et al. The Examiner now contends that one would have been motivated to do so because Vaccaro teaches that Sap C induces leakage of a vesicle comprising both PS and PE and that Egas teaches

that the effect of Saposin domain-like peptide on the leakage of phospholipid vesicle depends on the phospholipid composition, with higher effect in the presence of PA/PE/PS vesicles.

The Examiner now contends that one of ordinary skill in the art would have a reasonable expectation of success to modify the assay of Vaccaro (1993) to use vesicle comprising PE such as PA/PE/PS to study the effect of Sap C on the stimulation of glucosylceramidase activity because Vaccaro (1993) teaches the method, Vaccaro (1994) and Egas et at. teach how to make vesicles comprising PS and PE.

As set forth in the attached Rule 1.132 declaration by Dr. Xiaoyang Qi, the teachings of Vaccaro and O'Brien merely show the formation of phosphatidylserine (PS) and phosphatidylcholine (PC) phospholipid liposomal vesicles and then adding Saposin C (SapC) to the formulation, resulting in a surface interaction of the protein with the vesicles. A lipid/saposin vesicle formed by this method does *not* have the same structure and will *not* function the same and will *not* exhibit anti-tumor activity as with the vesicles of the present invention.

The present invention is not a case of simply forming a composition comprising a mixture of lipid nanovesicles and polypeptide but is a composition comprising a SapC-DOPS nanovesicle complex. The composition of the present invention comprises a SapC-DOPS nanovesicle complex and the formation of such a complex would be clear to one skilled in the art from the description of the present invention within the specification, especially as described in Example 2. This shows a composition comprising a SapC-DOPS nanovesicle complex and not just a mixture of nanovesicles and SapC suspended in a carrier.

That the methods and compositions described in the Vaccaro reference (FEBS 1993, 336(1): 159-162) are not the same as those described in the present application is obvious given that the Vaccaro reference actually shows that addition of SapC to DOPS-only liposomes alters the size and morphology of the liposomes to yield a different product. The liposomes, as shown in the electron micrographs of Fig. 6 in one of the publications (Vaccaro *et al.* FEBS Letters 349(1994)181-184), are a much larger liposome vesicle that is not a nanovescicle having SapC integrated within its structure.

The nanovesicles, made from the materials and methods of the present invention, are much smaller liposomes (generally about 200 nm or smaller) that exhibit anti-tumor activity. The liposomes of the Vaccaro reference are created first with SapC added after formation resulting in fused, larger sized PS/PC phospholipid vesicles that are up to 2000 nm in size or larger. This creates a different product where the polypeptide merely adheres to the surface of the large liposomes and renders liposome that fail to show significant anti-tumor activity.

As shown in the attached studies of the Qi Declaration, results show that the Saposin C polypeptide, when mixed with nanovesicles after the nanovesicles have been formed, does not exhibit the same effect as the SapC-DOPS nanovesicle complexes, formed by the processes of the present application. These results show that a co-treatment of Saposin C and the DOPS vesicles provide for no significant cancer cell killing (Table 1) and tumor targeting (Figure 1) effects.

Table 1.

Treatments of neuroblastoma (CHLA-20) cells with protein and/or lipid.

Human Cells	Cell Death (%)	
Cancer	**Untreated**	**SapC-DOPS**
Neuroblastomas: CHLA-20	13.8 ± 3.8	87.2 ± 0.7
Cancer	**Untreated**	**SapC and DOPS**
Neuroblastomas: CHLA-20	13.8 ± 3.8	20.6 ± 6.1
Cancer	**Untreated**	**DOPS**
Neuroblastomas: CHLA-20	13.8 ± 3.8	11.9 ± 3.4
Cancer	**Untreated**	**SapC**
Neuroblastomas: CHLA-20	13.8 ± 3.8	12.2 ± 1.6

As can be seen from the table, the experimental results show the following:

SapC-DOPS: nanovesicle complexes, significant killing effect.

SapC and DOPS: co-treatment of SapC and the DOPS vesicles, no significant killing effect.

DOPS: DOPS vesicles alone, no significant killing effect.

SapC: SapC alone, no significant killing effect.

Accordingly, it is submitted that the rejections under 35 U.S.C. 103 is not applicable to the claims of the present invention, as amended herein, and it is respectfully requested that they be withdrawn.

CONCLUSION

In light of the amendments and remarks made herein, it is respectfully submitted that the claims currently pending in the present application are in form for allowance. Accordingly, reconsideration of those claims, as amended herein, is earnestly solicited. Applicants encourage the Examiner to contact their representative, Stephen R. Albainy-Jenei at (513) 651-6839 or salbainyjenei@fbtlaw.com.

The Commissioner for Patents is hereby authorized to charge any deficiency or credit any overpayment of fees to Frost Brown Todd LLC Deposit Account No. 06-2226.

Respectfully submitted,

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